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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 08/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/755,747	BROOKES, ANTHONY J.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2004* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-18,20-31,33-44,46-52 and 67-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-18,20-31,33-44,46-52 and 67-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status

1. Claims 1-5, 7-18, 20-31, 33-44, 46-52, and 67-76 are pending.

Claims 1-5, 7-18, 20-31, 33-44, 46-52, and 67-76 are rejected.

Claim Rejections - 35 USC § 112

2. Claims 1-5, 7-18, 20-31, 33-44, 46-52, and 67-76 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As MPEP 2163.06 notes " If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

The amendment to include the term "monolayer" is new matter. The specification of the instant application was wordsearched, both by an optical character recognition of the specification in the computer version of the application as well as by a word search of the published application. The word "monolayer" as well as the broader term "layer" were both searched (including plurals) and no basis was found for these terms. The response confines itself to the bare statement that "no new matter has been added by the amendments or new claims (see page 14 of response)" but no specific support for

the term "monolayer" is identified in the response. Therefore, in the absence of any identified support for the term, the claims are rejected as containing new matter.

Response to Arguments – New matter Rejection

3. Applicant's arguments filed July 6, 2004 have been fully considered but they are not persuasive.

Applicant reiterates the argument regarding whether the term "monolayer" is new matter in this application. Applicant attempts to rely on caselaw to support the position that the term is not new matter. Applicant also attempts to rely upon other art, not necessarily demonstrated as prior art, which was not disclosed in the specification, and to which any reference in the specification was not limited. The specification did not name specific manufacturers or specific formulations, but rather generically referred to a particular plate. There is no question or argument from Applicant that the specification is entirely silent on the word "monolayer", that this word does not appear in the specification, and that the only possible route to find support is to provide evidence, such as the declaration rebutted above, which makes the term "monolayer" inherent in the 2-D hybridization system using streptavidin biotin.

So the entire question devolves on the issue of whether it is NECESSARILY the case that the streptavidin plate is a monolayer. As shown by Jordan et al, such a conclusion is not necessarily the case. Jordan et al demonstrate that such hybridization systems can form multiple layers of DNA, and need not necessarily result in DNA monolayers. In fact, figure 1 of Peluso, cited by Applicant, does not support the

conclusion that attachment is inherently limited to monolayers. Peluso simply provides an example where monolayers were formed.

When Applicant argues that the Strohner declaration was not given sufficient weight, this argument is not found persuasive because the declaration was specifically discussed and found nonpersuasive for the reasons of record. The response argues that a DNA monolayer was the inevitable result of the attachment to the streptavidin coated plates. However, as noted above, Jordan shows that monolayers are not inevitable. They may be the more likely result, but that is insufficient to provide support for a term that never appears in the specification.

Applicant argues that the molecular arrangement of Jordan is different than that disclosed in the specification. This is incorrect because NO ARRANGEMENT is disclosed in the specification. It is difficult to argue that something is different when the arrangement of Applicant appears in neither the specification nor the claims. When Applicant argues that Jordan teaches a monolayer, that is in direct contradiction to Jordan's own showing. As table 1 of Jordan clearly shows, the DNA can interact to form dendrimers which are not monolayers. While monolayers may certainly result under some circumstances with some DNA sources, other DNA sources will yield multilayer molecules.

Applicant relies upon a single short sentence to both inherently teach monolayers and to distinguish Jordan by arguing that the result of Jordan does not teach that monolayers are not inherent. This sentence cannot carry so much weight because it lacks any explicit limitation to any particular type of plate, and certainly lacks any

requirement that the biotin, the DNA or anything else form a monolayer. So the argument by Applicant that the result is the inherent and necessary result is not found persuasive and the rejection is maintained. For the same reasons, priority is not granted to the parent applications.

Priority

4. The current claims do not receive priority to the parent application GB 9821989.2 as well as PCT/GB99/03329 because those specifications do not provide descriptive support for monolayers. Therefore, prior art as of the instant filing date is applicable to the current claims.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-5, 8, 10-18, 21, 23-31, 34, 36-44, 47, 49-52, 67-71, 73, 74, and 76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stimpson et al (Proc. Natl. Acad. Sci. (1995) 92:6379-6383) in view of Wittwer (U.S. Patent 6,174,670).

Stimpson teaches a method of detecting DNA variation by monitoring the formation or dissociation of a of a complex (see abstract which states that "single base discrimination is facile") consisting of:

(a) a single strand of a DNA sequence (here the 15 mer oligonucleotide are attached to a glass solid support which is a monolayer of the nucleic acids, since each

is directly attached to the glass support itself and not some three dimensional structure; see page 6380, column 1, for example),

(b) an oligonucleotide specific for the single stranded DNA sequence specific for one allele of the variation and capable of hybridizing to the single strand (a) to form a duplex (see the biotinylated complementary sequences, table 1 and page 6380-81, subheading "Hybridization and staining for wave guide")

(c) a marker detection of the duplex structure of (a) plus (b) which forms a complex with the said duplex (here the selenium label, see page 6381, figure 1, for example),

which method comprises:

(1) steadily and progressively adjusting the temperature by 1°C increments (see figure 3, page 6382, where melting curves were made by increasing temperature incrementally),

(2) continually measuring an output signal indicative of the duplex formed from the strand (a) and probe (b) (see page 6382, figure 3) and

(3) recording the conditions at which a change in reaction output signal occurs which is attributable to formation or dissociation of the complex and is thereby correlated with the strength with which the probe (b) has hybridized to the single strand (a) (see page 6383, table 3, where the temperature at which the single base mismatch changes the signal).

Stimpson further teaches formation of two or more complexes, each with a probe specific for a different allele of the variaition, and observing their respective denaturing

or annealing conditions to distinguish alleles of the variation (see page 6382, figure 3, where two oligos, 23B and 24B are simultaneously tested).

Stimpson does not teach the use of a marker which is duplex specific in the analysis.

Wittwer et al teaches a method of detecting DNA variation by monitoring the formation or dissociation of a complex (abstract) consisting of:

(a) a single strand of a DNA sequence (here denatured genomic DNA (column 9, line 21) and/or denatured amplified PCR products, including an 81 basepair cystic fibrosis gene product (column 40, lines 58-67)) as well as many longer PCR products such as the 536 base pair b-globin sequence (column 47, line 24),

(b) an oligonucleotide specific for the single stranded DNA sequence (here either the primers used in PCR (column 41, lines 1-20) or pairs of fluorescently labeled oligonucleotide probes (column 9, lines 27-37)),

(c) a marker specific for the duplex structure of (a) plus (b) which forms a complex with the said duplex and reacts uniquely when interacting within the duplex (here either SYBR green, (see column 40, line 65) or the fluorescence resonance energy transfer pair of labels, which differentially fluoresce when in duplex or single stranded states (column 9, lines 27-37)),

which method comprises:

(1) "monitoring fluorescence while changing temperature at a rate of 0.1 degree C/second."(see column 15, lines 25-26).

(2) continually measuring an output signal indicative of interaction of the marker with duplex formed from the strand (a) and probe (b) (see column 9, lines 50-55 or column 41, lines 14-17 and figure 43) and

(3) recording the conditions at which a change in reaction output signal occurs which is attributable to formation or dissociation of the complex and is thereby correlated with the strength with which the probe (b) has hybridized to the single strand (a) (see page column 9, lines 55-59 or column 41, lines 14-17 and figure 43).

Column 14 details a similar assay for differentiating the Factor V Leiden mutation. Column 46 teaches the use of two or more complexes of the kind defined, each with a probe specific for a different allele of the mutation which multiple detection probes are distinguished by the different melting peaks (see column 46, lines 49-61). Wittwer further teaches measurement of the annealing based upon the first or second derivatives of the fluorescent melting curves (column 12 and columns 23-26) and expressly discusses measurement of the second order rate constant (see column 12).

Wittwer expressly teaches with regard to claims 67-70 that "The melting curves are easiest to visualize by plotting the negative derivative of fluorescence with respect to temperature vs temperature (-dF/dT vs T) (column 45, lines 10-14)". Thus, with regard to the negative derivative of the fluorescent measurement, Wittwer is teaching determining the presence of a peak. Wittwer is clearly showing the presence of peaks in figure 46 B, where the homozygous and heterozygous (termed match and mismatch in the claim) are separately identified using the negative derivative data analysis method.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the markers of Wittwer in the mutation detection method of Stimpson since Wittwer states "SYBR™ Green I is a preferred double strand specific dye for fluorescence monitoring of PCR, primarily because of superior sensitivity, arising from greater discrimination between double stranded and single stranded nucleic acid. SYBR™ Green I can be used in any amplification and is inexpensive. In addition, product specificity can be obtained by analysis of melting curves, as will be described momentarily (column 23, lines 9-16)". Thus, an ordinary practitioner would have been motivated to use SYBR™ Green I in the melting curve analytical method of Stimpson since Wittwer teaches that this intercalator is superior in sensitivity, is useful in the particular assay employed by Stimpson since the waveguides would detect the fluorescent label and is inexpensive.

7. Claims 1-5, 7, 8, 10-18, 20, 21, 23-31, 33, 34, 36-44, 46, 47, 49-52 and 67-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stimpson et al (Proc. Natl. Acad. Sci. (1995) 92:6379-6383) in view of Wittwer (U.S. Patent 6,174,670) and further in view of Heller et al (U.S. Patent 6,048,690).

Stimpson in view of Wittwer teach the limitations of claims 1-5, 8, 10-18, 21, 23-31, 34, 36-44, 47, 49-52, 67-71, 73, 74, and 76 as discussed above. Stimpson in view of Wittwer do not teach immobilization of the oligonucleotide using biotin-streptavidin.

Heller teaches immobilization of oligonucleotides to arrays using biotin-streptavidin for nucleic acid detection assays (column 16, lines 62-67).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the method of Heller in the detection method of Stimpson in view of Wittwer since Heller states "In this example, the first probe (a capture/quencher probe sequence) has two terminal functional groups, a 5'-terminal biotin group which allows the probe to be immobilized to the surface (permeation layer) of a microlocation test site on an active DNA chip or other hybridization device." (column 16, lines 62-67). An ordinary practitioner would have been motivated to use the biotin capture method in order to permit immobilization of probes to desired microlocations of DNA chips for the analytical method. Also, an ordinary practitioner would be motivated to select a known equivalent of the method of Stimpson for attachment of the nucleic acids to the array as Stimpson teaches biotin capture methods (see page 6380, column 2).

8. Claims 1-6, 8-19, 21-32, 34-45, 47-52, 67-71, 73, 74 and 76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stimpson et al (Proc. Natl. Acad. Sci. (1995) 92:6379-6383) in view of Wittwer (U.S. Patent 6,174,670) and further in view of Konrad et al (U.S. Patent 5,789,167).

Stimpson in view of Wittwer teach the limitations of claims 1-5, 8, 10-18, 21, 23-31, 34, 36-44, 47, 49-52, 67-71, 73, 74, and 76 as discussed above. Stimpson in view of Wittwer do not teach the use of Hepes buffer in hybridization.

Konrad teaches that " The conditions for hybridization of oligonucleotide sequences are well known. Generally, the hybridization step is either performed in a buffered aqueous salt solution at high temperature or in the presence of formamide at

lower temperature. The aqueous, high temperature procedure is typically carried out in a Tris buffer, such as 0.3M NaCl, 20 mM Tris -HCl, pH 6.8, at 67.degree. C. Other buffering systems such as hepes or glycine-NaOH and potassium phosphate buffers can be used. (column 14, lines 59-67)".

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the Hepes buffer of Konrad in the detection method of Stimpson in view of Wittwer since Konrad expressly teaches that Hepes buffer is an equivalent buffer for use in hybridization reactions.

Response to Arguments regarding 103 rejection

9. Applicant's arguments filed July 6, 2004 have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, Applicant reapplies a piecemeal analysis by saying that if one wanted to perform the method of Wittwer, one would use Wittwer, while if one wanted to detect variation, one would use Stimpson. It is the combination of these teachings that renders the claims obvious, and particularly the teaching by Wittwer that Sybr Green is a very sensitive detection molecule.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by

combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, specific motivation is provided in the rejection. In particular Wittwer states "SYBR™ Green I is a preferred double strand specific dye for fluorescence monitoring of PCR, primarily because of superior sensitivity, arising from greater discrimination between double stranded and single stranded nucleic acid. SYBR™ Green I can be used in any amplification and is inexpensive. In addition, product specificity can be obtained by analysis of melting curves, as will be described momentarily (column 23, lines 9-16)".

There can be no greater motivation than the detailed encomium provided by Wittwer, which represents a paean to the excellence of SYBR Green I. Such a statement clearly motivates the use of SYBR Green I in any amplification based assay to the ordinary practitioner. So when the ordinary practitioner looks at the motivation from Stimpson and Wittwer, there is clear motivation to detect using SYBR Green I.

With regard to Applicant's argument that there was no reasonable expectation of success to combine the Wittwer and Stimpson references, this requirement is derived from the caselaw. The Federal Circuit in In re O'Farrell, 853 F.2d 894, 903, 904 (Fed. Cir. 1988) noted

> "The admonition that "obvious to try" is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one

> possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. (citations omitted). In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. (citations omitted). Neither of these situations applies here."

Following the analysis of In re O'Farrell, This is not an instance where the prior art references of Wittwer and Stimpson suggest varying a variety of parameters. Here, Wittwer precisely, definitely and clearly suggests and motivates the use of SYBR Green I. Thus Wittwer expressly shows the expectation of success in using SYBR Green I for detection of DNA in amplification based assays. So there is specific guidance and a nearly 100% expectation of success, since Wittwer clearly demonstrates that SYBR Green I can be used with great success. With regard to the the issue of general guidance, both Wittwer and Stimpson give specific guidance as already noted to combine their methods. Thus, as in O'Farrell, neither of the "obvious to try" situations occurs here, since there is specific and direct teaching of the parameters of the invention with specific guidance to select SYBR GREEN I. Applicant continues by arguing incorrectly that the combination would not represent the invention, Since the prior art does not teach the "monolayer". This is incorrect because Stimpson is more a monolayer than Applicant because Stimpson directly binds to DNA to the support.

Applicant then reiterates the same arguments against the rejections over the dependant claims. These arguments are not persuasive for the reasons already given. Therefore these rejections are also maintained.

Conclusion

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
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Art Unit 1637
8/03/07